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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/733,776	12/12/2003	Mechthild Rieping	7601/80921	9536

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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1656	

MAIL DATE	DELIVERY MODE
10/24/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/733,776	RIEPING, MECHTHILD	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11,14,15,19,20,22,23 and 25-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *35-37* is/are allowed.

6)☒ Claim(s) *11,14,15,19,20,22,23,25 and 28-34* is/are rejected.

7)☒ Claim(s) *26 and 27* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] In view of the appeal brief filed on 7/24/07, PROSECUTION IS HEREBY REOPENED. A new ground of rejection is set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below:

PONNATHAPU ACHUTAMURTHY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

[2] Claims 11, 14-15, 19-20, 22-23, 25-37 are pending in the application.

[3] Appellant's arguments in the Appeal Brief filed on 7/24/07 ("Brief") in response to the Advisory Action mailed on 6/18/07 have been fully considered and are addressed below.

[4] The rejection of claims 11, 14-15, 19-20, 22-23, 25, and 28-34 under 35 U.S.C. 103(a) as being unpatentable over Volz (*Protein Sci* 8:2428-2437, 1999; cited in the IDS filed on 11/18/2004) in view of Enos-Berlage et al. (*J. Bacteriol* 180:6519-6528, 1998; cited in the IDS filed on 11/18/2004) is withdrawn. The rejection is withdrawn not in view of appellant's arguments, but in favor of the new rejection under 35 U.S.C. 103(a) as set forth below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

[5] Claim(s) 11, 14-15, 19-20, 22-23, 25, and 28-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Volz (*Protein Sci* 8:2428-2437, 1999; cited in the IDS filed on 11/18/2004) in view of Enos-Berlage et al. (*J. Bacteriol* 180:6519-6528, 1998; cited in the IDS filed on 11/18/2004; "Enos-Berlage"), Verkhovskaya et al. (*Microbiol.* 147:3005-3013, 2001; "Verkhovskaya"), and Promega Technical Bulletin No. 117 (September, 2002). The claims are drawn to a method for the production of an L-amino acid by culturing an *Escherichia* bacterium and recovering or isolating the L-amino acid; wherein the yjgF open reading frame of the bacterium has been modified

according to claim 11, wherein the modification results in an increased L-threonine production.

The reference of Volz teaches an attempt to ascertain the function of an *Escherichia coli yjgF* gene product (Yjgf) by analysis of its crystal structure (p. 2428, abstract) and that "[a]lthough the sequence-to-structure-to-function approach was not successful in this test case, the results suggest a variety of experiments that should complete the goal...More general experiments include determination of the phenotype of an organism (*E. coli, S. cerevisiae, or Caenorhabditis elegans*) after deletions of all YjgF paralogs. Preliminary results toward this approach with *S. typhimurium* have already been reported (Enos-Berlage et al., 1998)" (p. 2435, column 1, top). Volz teaches the sequence of *E. coli* YjgF (p. 2429). Although suggested by Volz, this reference does not teach an *E. coli* with a deleted *yjgF* gene, nor does the reference teach culturing of such *E. coli* or isolating an L-amino acid.

The reference of Enos-Berlage, which is cited by Volz, teaches a method of phenotyptic characterization of the *S. typhimurium yjgF* gene product using a ygjF-negative mutant created by inactivation of the *S. typhimurium yjgF* gene (p. 6519, abstract and 6520, column 2, top) and further teaches the sequence of *E. coli* YjgF polypeptide (p. 6523, Figure 3).

At the time of the invention, methods for gene inactivation in an *E. coli* bacterium were well-known in the prior art. For example, the reference of Verkhovskaya teaches a method for deleting a gene in *E. coli* by gene knockout, which method encompasses verification of genotype by PCR (see *Interruption of* yjcE *(GRN11 strain)* at p. 3006,

bridging columns 1-2), wherein the reference of Verkhovskaya teaches the genomic DNA was prepared by Wizard® DNA purification system. According to the Wizard® instructions in Promega Technical Bulletin No. 117, the method includes preparing an overnight bacterial culture (*e.g.,* p. 6, middle), centrifuging the culture to separate the cells from the liquid medium (*e.g.,* p. 3, step III.A.1), lysing the cells and centrifuging to remove cell debris (*e.g.,* p. 3, step III.A.2.-5.), and removing the lysate from the cell debris (*e.g.,* p. 4, step IV.A.2.).

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Volz, Enos-Berlage, Verkhovskaya, and Promega Technical Bulletin No. 117, to make an *E. coli* with deletion of a *yjgF* gene, culture the resulting mutant *E. coli,* and obtain a cell-free lysate thereof. One would have been motivated to do this because of the express suggestion of Volz as noted above, particularly as Volz is concerned with determining the function of an *E. coli* YjgF protein. One would have a reasonable expectation of success for making an *E. coli* with deletion of the *yjgF* gene, culture the resulting mutant *E. coli,* and prepare a cell-free lysate thereof because of the results of Enos-Berlage, Verkhovskaya, and Promega Technical Bulletin No. 117. Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to make an *E. coli* with deletion of a *yjgF* gene, culture the resulting mutant *E. coli,* and obtain a cell-free lysate thereof, which method would have necessarily resulted in practicing the methods of claims 11, 14-16, 19-20, 22-23, 25, and 28-34.

The following comments are provided in order to clarify the instant rejection. While the combination of cited references does not *expressly* teach recovery or isolation

of an L-amino acid from an *E. coli* with deletion of the *yjgF* gene or the culture medium thereof, by isolating a cell free lysate of *E. coli* with deletion of the *yjgF* gene (*e.g.,* p. 4, step IV.A.2. of Promega Technical Bulletin No. 117) or isolating the liquid medium from the *E. coli* cells with deletion of the yjgF gene (*e.g.,* p. 3, step III.A.1 of Promega Technical Bulletin No. 117), one would necessarily recover or isolate the L-amino acid in accordance with the claims, particularly as the specification (p. 4, lines 6-9) discloses, "isolation of the desired L-amino acid, constituents of the fermentation broth and/or the biomass in its entirety or portions (>0 to 100 %) thereof optionally remaining in the product." ("[T]he specification 'is always highly relevant to the claim construction analysis. Usually it is dispositive; it is the best single guide to the meaning of a disputed term.'" *Phillips v. AWH Corp.*, 415 F.3d 1303, 1315, 75 USPQ2d 1321, 1327 (Fed. Cir. 2005)). Also, while the combination of references fails to *expressly* teach the production of an L-amino acid, or the amino acid(s) recited in claims 15-16 and 30-34, in accordance with the evidence provided in the specification, this would be a necessary feature of culturing an *E. coli* with deletion of the *yjgF* gene as suggested by Volz.

RESPONSE TO ARGUMENT: Beginning at p. 4 of the Brief, appellant argues neither Volz nor Enos-Berlage is directed to fermentative production of amino acids. According to appellant (Brief at p. 4, middle) one of the main distinguishing features of the claimed invention is the step of isolation or recovery of amino acids from bacterial cultures. Appellant argues the examiner's inherency rationale is flawed factually (Brief at p. 5, top) because the references fail to teach culturing of cells with a *yjgF* mutation,

lysing cells, and preparing a lysate thereof. While appellant acknowledges the teachings of Enos-Berlage disclosing PCR amplification of genomic DNA, according to appellant, PCR amplification does not involve isolation of amino acids. Appellant argues the examiner's inherency rationale is flawed legally because: 1) inherency arguments are inappropriate for 103(a) rejections (Brief at p. 5, bottom), particularly as Enos-Berlage does not teach or suggest any relationship between *yjgF* mutation and increased amino acid production; 2) the teachings of Volz and Enos-Berlage are incompatible (Brief at p. 6, top); and 3) Enos-Berlage teaches away from using *ygjf* mutants for amino acid production because there is no evidence that the conditions under which the *Salmonella* mutants of Enos-Berlage were grown are conducive to amino acid production and Enos-Berlage suggests the *Salmonella ygjf* mutants are blocked in isoleucine production (Brief at p. 6, bottom).

Appellant's argument is not found persuasive. The examiner maintains the position that the claimed invention would have been obvious to one of ordinary skill in the art at the time of the invention in view of the combination of the Volz and Enos-Berlage references. There is no dispute that the references do not appear to be *expressly* concerned with fermentative production of L-amino acids. Also, there is no dispute that the references do not appear to be *expressly* concerned with isolation or recovery of L-amino acids. What appears to be in dispute is whether the method suggested by the combination of Volz and Enos-Berlage would have necessarily resulted in the claimed method. Although it is noted the rejection is now based on the additional references of Verkhovskaya, and Promega Technical Bulletin No. 117, to the

extent appellant's arguments apply to the instant rejection, such arguments have been addressed below.

Appellant argues that deletion of the *E. coli yjgF* gene using transposon-mediated mutagenesis, which is the method used by Enos-Berlage to mutate the *yjgF* gene of *S. typhumurium,* would not result in the production of a cell lysate. Initially, it is noted that this argument has yet to be presented during prosecution of this application. In response to this argument, it is noted that although Enos-Berlage do not *expressly* teach preparation of a cell lysate in the disclosed method, such would have been necessary for PCR as disclosed in *Localization of* yjgF *mutations by PCR amplification* at p. 6520, column 2, bottom. Also, preparation of a cell-free lysate is practiced in the method of Verkhovskaya in, *e.g.,* confirming the presence of the mutant genotype by PCR as taught by Verkhovskaya at p. 3006. Moreover, it is noted that production of a cell-free lysate is not required to inherently practice the claimed invention. For example, merely culturing an *E. coli* having a deletion of the *yjgF* gene, centrifuging the culture to separate the cells from the liquid medium (*e.g.,* p. 3, step III.A.1 of Promega Technical Bulletin No. 117), and pouring the supernatant away from the cells would fall within the scope of the claimed method, since this would necessarily purify or isolate the amino acid in the medium from the whole cells.

Addressing appellant's argument that an inherency rationale is inappropriate in an obvious rejection, appellant's attention is directed to MPEP 2112, which states (in relevant part), "[t]he express, implicit, and inherent disclosures of a prior art reference may be relied upon in the rejection of claims under 35 U.S.C. 102 or 103. 'The inherent

teaching of a prior art reference, a question of fact, arises both in the context of anticipation and obviousness.'" Even though the combination of references fails to *expressly* teach a relationship between a *ygjf* mutation and amino acid production, the *implicit* and *inherent* teachings of the prior art must nonetheless be considered in determining whether the claimed method would have been obvious at the time of the invention. In this case, the claimed method would necessarily result from practicing the method as suggested by the prior art.

As noted above, the reference of Volz expressly teaches, "[a]lthough the sequence-to-structure-to-function approach was not successful in this test case, the results suggest a variety of experiments that should complete the goal...More general experiments include determination of the phenotype of an organism (*E. coli, S. cerevisiae, or Caenorhabditis elegans*) after deletions of all YjgF paralogs. Preliminary results toward this approach with *S. typhimurium* already been reported (Enos-Berlage et al., 1998)" (p. 2435, column 1, top). Appellant argues the teachings of Volz and Enos-Berlage are incompatible (which argument has yet to be presented during prosecution), however, it is noted that in view of the above disclosure of Volz, one of ordinary skill in the art would recognize that the teachings of Volz and Enos-Berlage *are* compatible – each of the references seeks (at least in part) to determine the function of the YjgF polypeptide, albeit using distinct techniques and methodology. While it is acknowledged that Enos-Berlage is concerned with characterizing phenotype of *S. typhimurium* with a *yjgF* mutation, Volz nonetheless suggests such a similar analysis be applied to *E. coli.*

Although appellant argues there is no evidence that the *S. typhimurium* culture conditions as disclosed by Enos-Berlage are "conducive to amino acid production" (which argument has yet to be presented during prosecution), appellant has provided no evidence to the contrary. As such, appellant's argument appears to be mere conjecture. Regardless, it is noted that one of ordinary skill in the art would use conditions that are suitable for culturing of *E. coli,* not *S. typhimurium.* While culturing conditions for microbial L-amino acid production may be optimized relative to the conditions used for routine culturing of *E. coli,* one of ordinary skill in the art would recognize that standard culture medium nonetheless is suitable for growth of *E. coli*, and thus amino acid production by the *E. coli.* See, *e.g.,* the reference of Kruse et al. (*Appl. Microbiol. Biotechnol.* 59:205-210, 2002), which teaches that during routine growth of *E. coli,* culturing was performed in LB medium, while during production of L-threonine using the same *E. coli* strain, culturing was performed in a defined medium (p. 206 under *Bacteria and growth conditions for physiological studies*), however, there is no evidence of record that LB medium is not "conducive to amino acid production" by *E. coli.* See particularly MPEP 2145, which states, "[t]he arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997)."

Addressing appellant's argument that Enos-Berlage suggests the *Salmonella ygjf* mutants are blocked in isoleucine production (Brief at p. 6, bottom), it is noted that the claims are not limited to production of isoleucine. See, *e.g.,* claim 11, which broadly encompasses production of any L-amino acid. Moreover, since the examiner's

obviousness rationale is based on inherency and does not rely on a nexus between the *ygjF* and *E. coli* L-amino acid production, the noted teaching by Enos-Berlage do not negate the motivation to combine the cited references. In this case, the motivation to combine is provided by Volz, which suggests deleting a *ygjF* gene in *E. coli*, and by practicing the method suggested by the prior art, one of ordinary skill would have necessarily practiced the claimed methods.

Conclusion

[6] Status of the claims:

Claims 11, 14-15, 19-20, 22-23, and 25-37 are pending.

Claims 11, 14-15, 19-20, 22-23, 25, and 28-34 are rejected.

Claims 26-27 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 35-37 appear to be in a condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

David J. Steadman, Ph.D.
Primary Examiner
Art Unit 1656